Hydrogel-Electrospun Fiber Mat Composites as Controlled Delivery Systems for Nerve Regeneration

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Statement of Purpose: Approximately 11,000 persons annually incur spinal cord injury (SCI) in the US. Unfortunately, no effective treatment currently exists for SCI. Tissue engineering offers one possible treatement strategy, and several research groups have examined polymers as neural tissue engineering scaffolds. One such system is the biocompatible and biodegradable PEG-polyester hydrogel, which can serve as both scaffolds and controlled delivery systems. These polymers are formed through photo-crosslinking, permitting hydrogels to be formed in situ. As such, hydrogels can be easily conformed to a desired shape and the encapsulated molecules can be uniformly distributed. Thus, combining PEG-polyester hydrogels with soluble factors, which support cell adhesion, neuron survival, and neurite extension, provides a potential method to encourage robust nerve regeneration.

However, in previous work[1], we have shown that these systems produce rapid early release (initial burst) with subsequent non-linear release over the duration of ~1 month. This is substantially less than our target of near constant release for 2-3 months, which is the duration thought to be necessary to overcome the acute immune reaction to injury. Here we present a new system: PEGPCL hydrogels combined with hydrophobic electrospun fiber mats (EFMs) that can be applied to controlled drug-delivery. Combining PEGPCL hydrogels with EFMs reduces the initial burst dramatically, extends release duration, and produces a more linear release profile. In addition, EFMs add topographical features to the composite scaffold, which is expected to encourage cellular adhesion, surface migration, and proliferation.

Methods: Diacryl poly (ethylene glycol)- poly (ε-caprolactone) (PEGPCL) copolymer was synthesized following a method similar to that of Hubbell *et al.*[2]. Fourier transform infrared spectroscopy (FT-IR) and nuclear magnetic resonance spectroscopy (NMR) were applied to characterize PEGPCL copolymer. Poly (ε-caprolactone) (PCL)-based fiber mats were prepared by electrospinning and characterized by scanning electron microscopy (SEM). PEGPCL hydrogels, and two different sandwich-like hydrogel-electrospun fiber mat composites (Composite A: Gel+EFM+Gel; Composite B: EFM+Gel+EFM) were constructed under UV exposure. Bovine serum albumin (BSA) was introduced into these systems for *in vitro* release study. BSA release was quantified using the Bradford protein assay and electrophoresis. Additionally, nerve growth factor (NGF) was incorporated into Composite B and the response of neural cells (i.e. PC12 cells) to the extended NGF release was studied. Phase contrast microscopy was used for investigating PC12 cells' neurite density and extension.

Results: The FT-IR and NMR spectra of PEGPCL confirmed successful copolymer synthesis. The yield of the final diacryl-PEGPCL was ~85% according to NMR. PCL electrospun fiber mats exhibited randomized fiber sizes (~0.6-5 μm) and orientations in SEM. These materials were used to form sandwich composites for drug release studies. There was no remarkable difference between the release profiles of PEGPCL hydrogel and Composite A (Gel+EFM+Gel). After a modest initial burst (~20%), BSA was released for ~40 days. Composite B (EFM+Gel+EFM) provided a more linear sustained BSA release for ~70 days without a noticeable initial burst. In the presence of NGF-releasing Composite B (EFM+Gel+EFM), the neurite density and extension of PC12 cells increased significantly, which confirmed the potential application of this hydrogel-electrospun fiber mat composites in nerve regeneration.

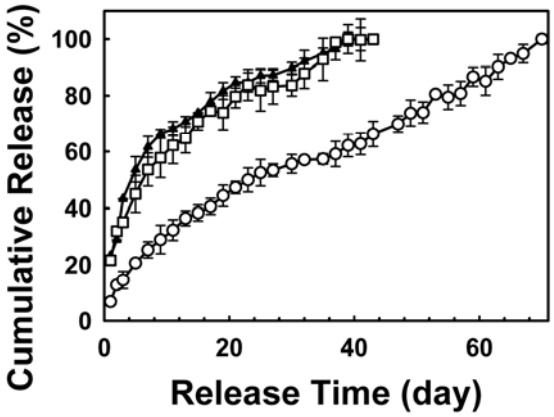

Figure 1. *In vitro* release profiles of BSA from (▲) PEGPCL hydrogels, (□) Composite A (Gel+EFM+Gel), and (○) Composite B (EFM+Gel+EFM)

Conclusions: The combination of these two types of biomaterial matrices: hydrogel and electrospun fiber mats, is a new strategy in tissue engineering. We hypothesize that two factors of the EFMs alter drug release: (1) thickness of the mat provides a diffusion barrier and (2) hydrophobic character of the mat delays hydrophilic drug release. By changing the number and position of PCL EFMs in the composite system, the release profile of a biomolecule could be altered significantly. Also, multiple active biomolecules could be separately introduced into different hydrogel layers (divided by PCL mats) in a modified composite structure, with different release profiles achieved simultaneously or with directional selectivity.

References:

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